Genetic Epidemiology 26: 125–131 (2004)

A Trisomic Transmission Disequilibrium Test

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Certain congenital disorders that are rare in the general population are quite common in individuals with trisomic conditions. For example, complete atrioventricular septal defect occurs in about 20% of individuals with Down syndrome, an approximately 500-fold increase in risk as compared to individuals without Down syndrome. Genetic variation on the chromosome involved in the trisomy may affect susceptibility to these trisomy-specific disorders. That is, increased dosage of a variant may be directly involved in increasing the risk of a disorder, or it may be indirectly involved by causing up- or downregulation of other genes. As in standard disomic gene-mapping, one can search for genes using linkage or association methods. Within association methods, one can consider case-control methods or family-based control methods such as the transmission disequilibrium test (TDT). Most gene-mapping methods need to be substantially redesigned for use with trisomic data. In this paper, we present a ''trisomic TDT'', a statistical method of testing for nonrandom transmission of alleles from parents to trisomic children. We demonstrate the method on a dataset of parent-child trios in which the child has Down syndrome. *Genet Epidemiol* 26:125–131, 2004. © 2004 Wiley-Liss, Inc.

Key words: trisomy; Down syndrome; TDT; association testing

Grant sponsor: NIH; Grant number: RO1 HD21341, RO1 HD38979.
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Received 11 July 2003; Accepted 22 August 2003
Published online in Wiley InterScience (www.interscience.wiley.com)
DOI: 10.1002/gepi.10302

INTRODUCTION

Although mental retardation is a consistent hallmark of all trisomic conditions, there are other disorders that are highly associated with specific trisomies. Examples include heart defects, leukemia, and duodenal atresia in trisomy 21 [Epstein, 2001]. Even among individuals with a specific trisomy, however, these disorders are not universal. Three factors have been proposed to explain the variability among individuals with a specific trisomy: 1) stochastic factors, 2) extrinsic factors, and 3) genetic differences [Epstein, 1993]. Stochastic factors refer to the inherent variability normally present in any developmental process so that, with all else being equal, more than one outcome is possible. Extrinsic factors include variation in maternal and environmental exposures. Lastly, genetic variation either on the chromosome involved in the trisomy or on another chromosome may affect susceptibility.

We previously proposed a linkage method to identify genes on the trisomic chromosome that increase susceptibility to specific disorders. An unusual feature of trisomic linkage testing is that studies are possible with only a single trisomic child, since the two chromosomes with the same parental origin provide linkage map information. Our approach was based on a hypothesis similar to that described by Engel [1980]. Specifically, we proposed that ''hyperdosage'' resulting from normal allelic differences explains some of the phenotypic variation in a trisomic condition [Feingold et al., 1995; Lamb et al., 1996]. Thus, a proportion of trisomic genotypes (and possibly rare disomic genotypes) cause a threshold to be exceeded, resulting in a particular phenotype. In the affected individual, the defect is due to the presence of two identical copies of a susceptibility allele, inherited from a heterozygous parent. This ''reduction to homozygosity'' or ''disomic homozygosity" for a susceptibility allele can arise in many ways: 1) from mitotic nondisjuntion,

resulting in disomic homozygosity for the entire chromosome; 2) from an error in meiosis II, resulting in disomic homozygosity from the centromere to the most proximal recombination event; or 3) from meiosis I nondisjunction, resulting in disomic homozygosity distal to a recombination event. Regardless of the exact mechanism, individuals with trisomy and a particular phenotypic defect are predicted to show greater-than-expected levels of disomic homozygosity in the chromosome region containing a susceptibility gene. We proposed a simple strategy, similar to that used in linkage studies using affected relative pairs, to identify the region of maximal disomic homozygosity [Feingold et al., 1995].

With the current availabilty of the human genome sequence, as well as substantial (and ever-improving) information about genes and polymorphisms, it is now timely to consider *association* methods for detecting susceptibility genes for disorders related to trisomic conditions. Whole-chromosome scans of the trisomic chromosome are within the realm of feasibility. As in standard disomic gene-mapping, association studies can be divided into population-based case-control studies and family-based control studies. By a "family-based control" method, we mean any test that conditions on parental (or other family) genotypes and tests for segregation distortion in the alleles that are passed to the children. For simplicity, we refer to such tests for the remainder of this paper as transmission disequilibrium tests (TDTs). The advantage of TDTs is that they are robust to population stratification, assortative mating, and other factors that can distort the parental distribution. The downside of TDTs is that they are not able to draw any power from the distribution of the *parental* genotypes. To take an extreme example, imagine a simple genetic disorder caused by a rare dominant allele B. If we collect case-parent trios, almost all parental pairs will include exactly one B allele. A TDT conditions on the parental genotypes and thus eliminates this important information, whereas a χ^2 test for a case-control comparison of the offspring will implicitly draw power from the distorted parental distribution.

In general, disomic gene-mapping methods are not directly applicable to trisomic individuals, but trisomic methods can be derived using similar principles. As discussed above, linkage methods for trisomy were developed by Feingold et al. [1995] and Lamb et al. [1996]. Case-control comparisons of trisomic individuals do not require special methods, except that they must be done by genotype rather than by allele, since the alleles are not independent. (Testing by genotype is probably preferable in disomic data as well; see Sasieni [1997]). In this paper, we fill out the complement of trisomic mapping methods by developing a trisomic TDT. We concentrate on methods for binary traits, but methods for quantitative traits are also possible.

The standard disomic TDT, in its simplest formulation [e.g., Spielman et al., 1993; Schaid and Sommer, 1994], can be thought of as follows. The unit of study is an individual who is affected with the trait of interest, along with both parents. The case and parents are genotyped at a diallelic marker. Each heterozygous parent provides an independent piece of data. We tally the alleles passed from the heterozygous parents to the affected offspring, and test whether the segregation ratio of the two alleles is 50/50. If the segregation is nonrandom, we conclude that an allele at or near the marker is probably affecting risk for the trait we selected on. Under standard simple assumptions, the TDT test statistic is proportional to $(1-2\theta)\delta$, where θ is the recombination fraction and δ is the association measure [Ewens and Spielman, 1995]. However, we must always be aware that simple models might not be correct; we could be picking up segregation distortion that has nothing to do with the trait. Apparent segregation distortion can even be caused by genotyping errors [Gordon et al., 2001; Mitchell et al., 2003]. A careful application of the TDT includes a ''control'' sample of unaffected children and parents, in order to make sure that any observed segregation distortion is seen only in the affected group.

In the trisomic case, it is even less appropriate to blithely assume that any segregation distortion we observe is due to the trait, because we must consider the issue of survival to term. For example, since live-born babies with Down syndrome account for only about 20% of clinically recognized trisomy 21 conceptuses [Hassold and Jacobs, 1984], we have to take seriously the possibility that there could be gene-specific selection effects. If survival of the fetus is affected by specific genes on chromosome 21, then we will observe segregation distortion at those loci in a sample of live-born individuals with, say, a congenital heart defect, even if those genes have nothing to do with the heart defect. That is, the selection and disease-association parameters are

confounded. The trisomic TDT that we propose here can be applied to either a control sample (trios in which the child is trisomic but has no other specific phenotype), or a case sample (trios in which the child is trisomic and additionally has some particular phenotype). If the test is applied to a control sample, any segregation distortion that is detected can be interpreted as a selection effect, i.e., as evidence that variation at or near this locus is associated with survival of the trisomic embryo. If the test is applied to a case sample, we must interpret segregation distortion as an unknown combination of selection effect and effect on the trait we are studying. There can also be selection effects *due to* the trait, e.g., if some defects are severe enough to cause the fetus to spontaneously abort. If we apply the test to both case and control samples, we can avoid the confounding, and differentiate selection and trait effects.

In developing a trisomic TDT, two issues arise that are specific to trisomy and that change the form of the test substantially. The first is that one parent is contributing two alleles, and the other parent is contributing only one. Thus contributions of the two parents cannot be considered symmetrically as they are in the standard TDT. We deal with this issue by developing a test that is based on the genotypes of the offspring rather than on the separate allelic contributions of the two parents. The second issue is that the two alleles contributed by the nondisjoining parent are not independent. That is, depending on the type of nondisjunction event (meiosis I or meiosis II error) and the location of the marker relative to the centromere, the two alleles, contributed by the nondisjoining parent may be duplicates of one parental allele, or they may be two separate parental alleles. This creates a dependence between the offspring alleles that is a function of the genetic map. In disomic data, alleleic association parameters and genetic map/linkage parameters are generally orthogonal, and can be estimated and tested completely separately. In trisomic data, they are dependent, and this dependence must be incorporated into the TDT. In our TDT, we estimate the map parameters along with the association parameters, but the test could be adapted to use map parameters that are known from other sources (see Discussion).

Taking all of these complications into consideration, the final form of our test is a likelihood ratio test comparing the likelihood of the data under a random segregation model to the likelihood of the data under a model that allows for selection and/or effects on the trait. Below, we outline the model. We then describe the test, and finally demonstrate it on an example ''control'' dataset of trios in which the offspring has Down syndrome but no other specific variable phenotype.

THE MODEL

Assume a biallelic marker locus with alleles labelled ''1'' and ''2.'' The association parameters in our model are

w_0=probability of survival and affectedness of a conceptus with genotype 111,
w_1=probability of survival and affectedness of a conceptus with genotype 112,
w_2=probability of survival and affectedness of a conceptus with genotype 122, and
w_3=probability of survival and affectedness of a conceptus with genotype 222.

We assume that $w_0=1$, and that the other ws are relative parameters, because we can never estimate all four of them with data only from live-born individuals. This means that w_1, w_2, and w_3 can take any value greater than zero. The w parameters do not depend on the parent of origin or stage of origin of the trisomy.

As previously discussed, the alleles transmitted to the trisomic offspring are dependent on the genetic map. Let ''NDJP'' indicate the nondisjoining parent and ''CDJP'' indicate the correctly disjoining parent. The map parameter we use is h, the probability that the two chromosomes contributed by the NDJP are reduced to homozygosity (derived from the same parental chromosome) at this marker *in a conceptus*. Our parameter h has a straightforward relationship to the usual trisomic genetic map parameter, y. In a meiosis I nondisjunction case, $h=y/2$, where y is the map parameter between the centromere and the marker being tested. In a meiosis II nondisjunction case, $h=1-y$. For more discussion of genetic maps in trisomy see, for example, Chakravarti and Slaugenhaupt [1987] or Feingold et al. [2000]. There is strong evidence for most trisomies that the genetic map depends on the parent of origin and the stage of origin of the trisomy [Hassold and Hunt, 2001]. We indicate this by using $h_{m\mathrm{I}}$ for a maternal meiosis I error, $h_{m\mathrm{II}}$ for a maternal

meiosis II error, $h_{p\mathrm{I}}$ for a paternal meiosis I error, and $h_{p\mathrm{II}}$ for a paternal meiosis II error.

Given parental genotypes, the probability of a conceptus of each genotype depends only on h. For example, suppose the mating type is 11×12, where the 12 parent is the NDJP. Then the CDJP must contribute a 1 allele. The NDJP contributes 12 if the two chromosomes are not reduced to homozygosity, and 11 or 22 if the two chromosomes are reduced to homozygosity. Thus the possible conceptus genotypes and probabilities are

$$P(\text{child is } 111) = P(\text{NDJP contributes } 11) = h/2,$$
$$P(\text{child is } 112) = P(\text{NDJP contributes } 12) = 1 - h,$$
and
$$P(\text{child is } 122) = P(\text{NDJP contributes } 22) = h/2.$$

To account for survival and to extrapolate from conceptuses to live-born individuals, we multiply these probabilities by the w parameters (assuming that w_0=1), which yields the unnormalized probabilities

$$P(\text{child is } 111) = h/2,$$
$$P(\text{child is } 112) = w_1(1 - h), \text{and}$$
$$P(\text{child is } 122) = w_2(h/2).$$

Normalizing so that the sum of the probabilities is one yields the expressions shown in Table I. The example above is the second mating type shown in Table I.

THE TEST

We use a likelihood ratio test with the model described above to test the null hypothesis that w_1=w_2=w_3=1, i.e., that there is no selection/trait effect. We use a completely unconstrained alternative hypothesis. For a control sample, one could potentially get more power by constraining the w parameters to be ordered, but this is probably not appropriate for a case sample, because there might be combinations of selection and trait effects. For example, suppose 99% of 111s die and the remainder are affected, 50% of 112s die and the remainder are affected, 30% of 122s die and 40% of those who live are affected, and no 222s die but 60% are affected. Then we have w_1=0.5/0.01=50, w_2=(0.7)(0.4)/0.01=28, and w_3=(1.0)(0.6)/0.01=60.

The likelihood is constructed as follows. Each mating type shown in Table I gives us a multinomial likelihood. These multinomial likelihoods are multiplied together to form the overall likelihood. Each type of nondisjunction error (mI, mII, pI, pII) is tallied separately because the h parameters are different (if enough markers are typed, one generally knows which subgroup each case belongs to). So there is a total of 5 mating types $\times$ 4 error types=20 multinomial likelihoods that are multiplied together to get the final likelihood. The total number of independent data points in the 20 multinomials is 9 data points $\times$ 4 error types=36. The total number of parameters

TABLE I. Probabilities of offspring genotypes, given parental genotypes

NDJP[a]	CDJP[b]	Child	Probability of child genotype, given parental genotypes
11	12	111	$(1/2)/[1/2+w_1/2]$
		112	$(w_1/2)/[1/2+w_1/2]$
12	11	111	$(h/2)/[(h/2)+w_1(1-h)+w_2(h/2)]$
		112	$w_1(1-h)/[(h/2)+w_1(1-h)+w_2(h/2)]$
		122	$w_2(h/2)/[(h/2)+w_1(1-h)+w_2(h/2)]$
12	12	111	$(h/4)/[h/4+w_1(1/2-h/4)+w_2(1/2-h/4)+w_3(h/4)]$
		112	$w_1(1/2-h/4)/[h/4+w_1(1/2-h/4) +w_2(1/2-h/4)+w_3(h/4)]$
		122	$w_2(1/2-h/4)/[h/4+w_1(1/2-h/4)+w_2(1/2-h/4)+w_3(h/4)]$
		222	$w_3(h/4)/[h/4+w_1(1/2-h/4)+w_2(1/2-h/4)+w_3(h/4)]$
12	22	112	$w_1(h/2)/[w_1(h/2)+w_2(1-h)+w_3(h/2)]$
		122	$w_2(1-h)/[w_1(h/2)+w_2(1-h)+w_3(h/2)]$
		222	$w_3(h/2)/[w_1(h/2)+w_2(1-h)+w_3(h/2)]$
22	12	122	$(w_2/2)/[w_2/2+w_3/2]$
		222	$(w_3/2)/[w_2/2+w_3/2]$

[a]NDJP is nondisjoining parent.
[b]CDJP is correctly disjoining parent.

being estimated under the alternative hypothesis is 3 w parameters+4 h parameters=7. In actual use, not all mating types and/or error types will necessarily be included in a given dataset. For example, if one allele is relatively rare, one is unlikely to observe intercross matings.

Under the null hypothesis, the w parameters disappear from the likelihood, and we can easily specify the maximum likelihood estimates of the h parameters. These are equivalent to the standard two-point centromeric mapping estimates as described, for example, by Feingold et al. [2000]. Under the alternative hypothesis, the likelihood must be maximized numerically. Because of the constraints on the parameters $(0 \leq h \leq 1, w_1 \geq 0, w_2 \geq 0, w_3 \geq 0)$, we used the L-BFGS-B algorithm [Byrd et al., 1995; Zhu et al., 1997]. We wrote a FORTRAN program (available on request) to maximize the likelihoods and perform the likelihood ratio test. The χ^2 test of the likelihood ratio has three degrees of freedom. We tested our software extensively on simulated and real data. The maximization appears to be extremely robust, and the starting values do not appear to matter. The one complication that arose in real datasets is that when the sample size is very small and/or one allele is rare, some mating types will not be represented, and it may not be possible to estimate all parameters.

DATA EXAMPLE

We applied our TDT to data from a single single-nucleotide polymorphism (SNP) genotyped in 43 control trios in which the offspring is affected with Down syndrome but does not have any additional specific disorder. The sample set for this study was drawn from the larger study of live births with free trisomy born and ascertained in the five-county metropolitan area of Atlanta, Georgia [Freeman et al., 1998]. Blood was obtained on mother, father, and proband for DNA extraction. Genotypes used for this sample set were obtained from a single SNP, rs874221 (http://www.ncbi.nlm.nih.gov/SNP/index.html), genotyped within SH3BGR. SH3BGR is found expressed in fetal heart tissue [Egeo et al., 2000] and lies within the proposed critical region for DS-associated congenital heart defects [Korenberg et al., 1994]. The SNP was genotyped by Pyrosequencing™, which adequately genotypes trisomic alleles.

The dataset is shown in Table II. Only nondisjunctions of maternal origin are included, because there are very few paternal cases in the sample. When we apply our software to this dataset, we get the parameter estimates shown in Table III. The null hypothesis for this analysis is that there is no viability selection due to genes at or near this locus. If the null hypothesis were true, we would expect to see values of the w parameters near 1.0 in the alternative hypothesis column. That is, the best-fitting model would be equivalent to the null hypothesis. We would also expect to see similar values of the h parameters in the two columns. If the alternative hypothesis were true, we would expect to see values of the w parameters different from 1.0, and values of the h parameters that differed between the two columns. The reason the h parameters would differ between

TABLE II. Example dataset

NDJP[a]	CDJP[b]	Child	mI[c]	mII[d]
11	12	111	4	1
		112	5	1
12	11	111	0	0
		112	9	3
		122	1	0
12	12	111	0	0
		112	5	2
		122	6	1
		222	0	2
12	22	112	1	0
		122	0	0
		222	0	0
22	12	122	2	0
		222	0	0

[a]NDJP is nondisjoining parent.
[b]CDJP is correctly disjoining parent.
[c]Maternal meiosis I cases.
[d]Maternal meiosis II cases.

TABLE III. Parameter estimates for example dataset

Parameter	Null hypothesis	Alternative hypothesis
w_1	1.0[a]	1.98
w_2	1.0[a]	1.74
w_3	1.0[a]	1.74
$h_{m\mathrm{I}}$	0.12	0.16
$h_{m\mathrm{II}}$	0.32	0.39

[a]These parameter values are specified under null hypothesis, not estimated.

the two columns under the alternative hypothesis is the previously discussed counfounding of the linkage and association parameters. If in fact there is association (selection), but we fit a model that does not account for it, we will misestimate the linkage parameters. (As an aside, note that this implies that standard trisomic linkage mapping methods, such as those described in Feingold et al. [2000], are incorrect in the presence of selection.)

Our results are relatively consistent with the null hypothesis, though the small sample size means that this analysis is far from conclusive. The estimates of h parameters are similar between the null and alternative hypotheses. The alternative hypothesis estimates of the w parameters are on the order of 2, indicating that a fetus with genotype 112, 122, or 222 is approximately twice as likely as a fetus with genotype 111 to survive to birth and be affected by a congenital heart defect. However, the value of the χ^2 statistic for the likelihood ratio test is 1.58, giving a P-value of 0.66 (3 df).

DISCUSSION

We present a TDT for trisomic data which can be used to detect selection effects of a locus, effects on a trait, or both. Given that we currently have little information about specific effects of genes with respect to survival of a trisomic fetus, we recommend that this test not be applied to case trios without also using control trios. Collecting both case and control trios also allows one to directly compare the genotype frequencies of the case and control offspring. Additional tests that could be applied to such a dataset include case-control comparisons of parental genotypes and tests of Hardy-Weinberg equilibrium in both offspring and parents.

One of the most important areas for further development of this work is the method for dealing with the map parameters (h parameters). In our example dataset, the map parameters are being estimated from an extremely small sample, i.e., a subset of cases selected from a larger population. It may be more appropriate to estimate h parameters from that larger dataset and use them in the TDT. Computationally this would be simple. However, if there are locus-specific selection effects in the larger dataset, the h estimates will be incorrect. If future study of control datasets using our TDT shows that selection effects are not important, then map parameters estimated from a large control dataset can be used in TDT studies of cases. Even if one must estimate the map parameters as a part of the TDT, the estimation could probably be improved with a multipoint procedure. If a number of markers very close together are being tested, one could expand our model to include all loci simultaneously, with separate w parameters at each locus but the same h parameter. One could even estimate different h parameters at each locus (i.e., estimate the entire linkage map simultaneously with the association parameters), though this would be computationally challenging.

Another obvious extension of our method is to consider markers with more than two alleles. The standard TDT extends to multialleleic markers by doing separate tests to each allele vs. all the others. P-values must be adjusted accordingly [e.g., Betensky and Rabinowitz, 2000]. It might be possible to take that approach here, though it is not entirely clear how to execute a correct P-value adjustment or how to interpret the estimates of h parameters.

Finally, it is also possible to extend our method to directly compare association parameters between case and control samples, rather than comparing each of them separately to random segregation. Such a two-sample test looks for effects on the trait while controlling for selection effects. To implement a two-sample test, we define the w parameters as survival probabilities, and define new "c" parameters for each genotype as the conditional probabilities of affectedness given survival. We fit our model as presented previously to the *control* data. Simultaneously, we fit the *case* data to the same model, but with the product wc in place of each w (so wc is the probability of a live-born affected offspring). This produces separate estimates of the w parameters and the c parameters, and we can test the c parameters (trait effect parameters) while treating the w parameters (selection parameters) as nuisance parameters. We feel that a two-sample test will probably be more appropriate sometime in the future, when selection effects in trisomy are better understood; at this point, it seems to us to be more informative to test cases and controls separately.

ACKNOWLEDGMENTS

This work was supported by NIH grants R01 HD21341 (to T. Hassold) and R01 HD38979 (S.L.S.).

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